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Investor science conference call
AASLD 2023

IPSEN
Innovation for patient care

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For patients & society

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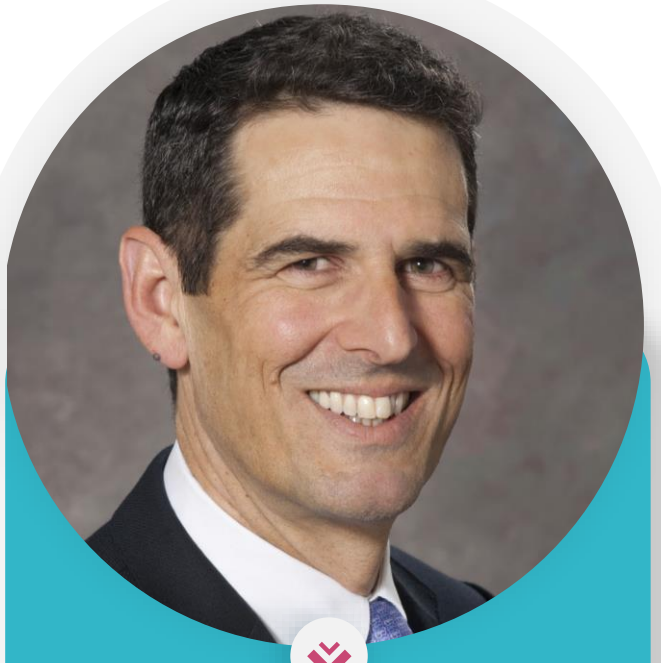
Speakers

Jennifer Schranz
SVP, Global Head Rare Disease Research & Development



Dr. Christopher L. Bowlus
Lena Valente Professor and Chief of the Division of Gastroenterology and Hepatology at the University of California Davis

David Loew
Chief Executive Officer

Jennifer Schranz

SVP, Global Head Rare Diseases Research & Development

Bringing transformative first-in-class, best-in-class medicines to patients

Oncology

Strengthening the position

Rare Disease

Expanding the scope

Neuroscience

Excelling and accelerating

Recent external innovation

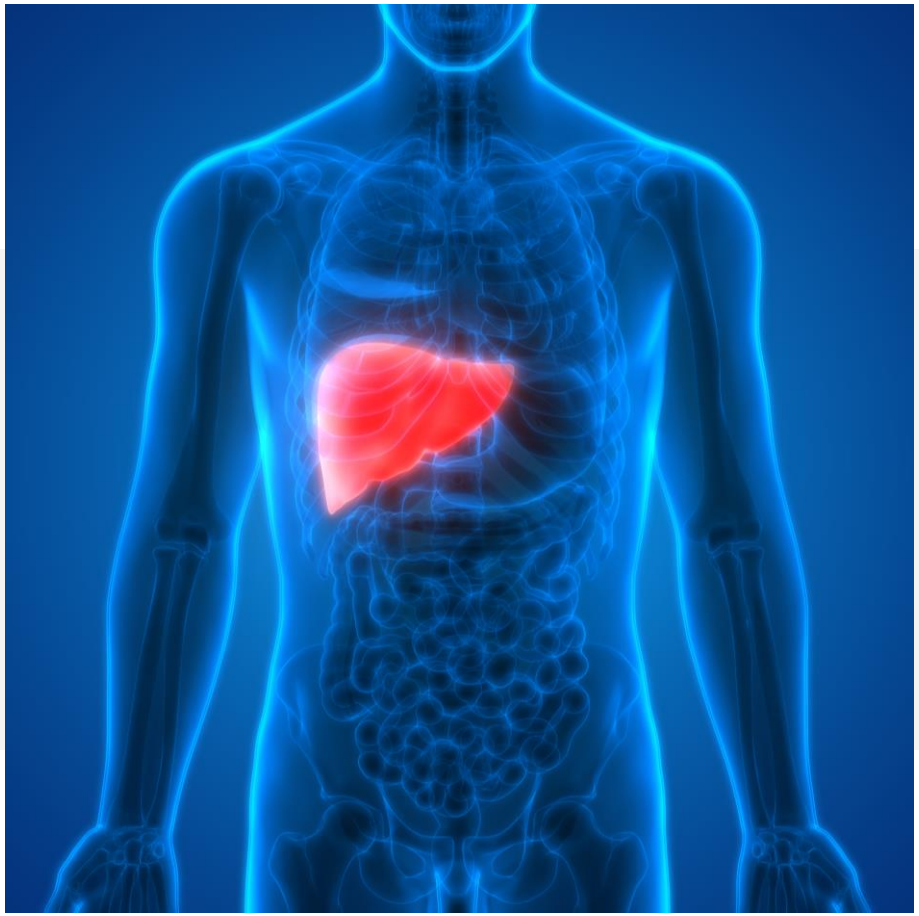
Transactions across rare cholestatic liver disease

Five potential rare cholestatic disease indications

IPSEN
Innovation for patient care

Ipsen at AASLD 2023

Growing presence in rare cholestatic liver disease



Demonstrating strength & expertise in understanding pathophysiology of rare cholestatic liver diseases

Eleven abstracts accepted for presentation
Two late-breakers

Furthering scientific understanding across several underserved rare cholestatic liver diseases, including:

PBC ALGS PFIC

Showcasing Bylvay® & elafibranor

PBC: primary biliary cholangitis; **ALGS**: Alagille syndrome; **PFIC**: progressive familial intrahepatic cholestasis.

Dr. Christopher L. Bowlus

Lena Valente Professor and Chief of the Division of Gastroenterology and Hepatology at the University of California Davis

Efficacy and safety of elafibranor in primary biliary cholangitis: Results from the ELATIVE™ double-blind, randomized, placebo-controlled phase 3 trial

Christopher L. Bowlus,[1] Kris V. Kowdley,[2,3] Cynthia Levy,[4] Ulus Akarca,[5] Mario Reis Alvares-da-Silva,[6] Pietro Andreone,[7] Marco Arrese,[8] Christophe Corpechot,[9] Sven Francque,[10,11] Michael A. Heneghan,[12] Pietro Invernizzi,[13,14] David Jones,[15] Frederik C. Kruger,[16,17] Eric Lawitz,[18] Marlyn J. Mayo,[19] Mitchell L. Shiffman,[20] Mark G. Swain,[21] José Miguel Valera,[22] Victor Vargas,[23] John M. Vierling,[24] Alejandra Villamil,[25] Carol Addy,[26] Julie Dietrich,[26] Jean-Michel Germain,[27] Sarah Mazain,[28] Dragutin Rafailovic,[27] Bachirou Taddé,[27] Benjamin Miller,[29] Jianfen Shu,[29] Claudia O. Zein,[29] Jörn M. Schattenberg,[30] and the ELATIVE™ Study Group

Presented at The Liver Meeting, AASLD 2023 | Boston, MA, USA | November 10–14 2023

#48490

Background

- **Primary biliary cholangitis (PBC)** is a rare, autoimmune, chronic cholestatic liver disease that occurs predominantly in women >40 years[1–3]

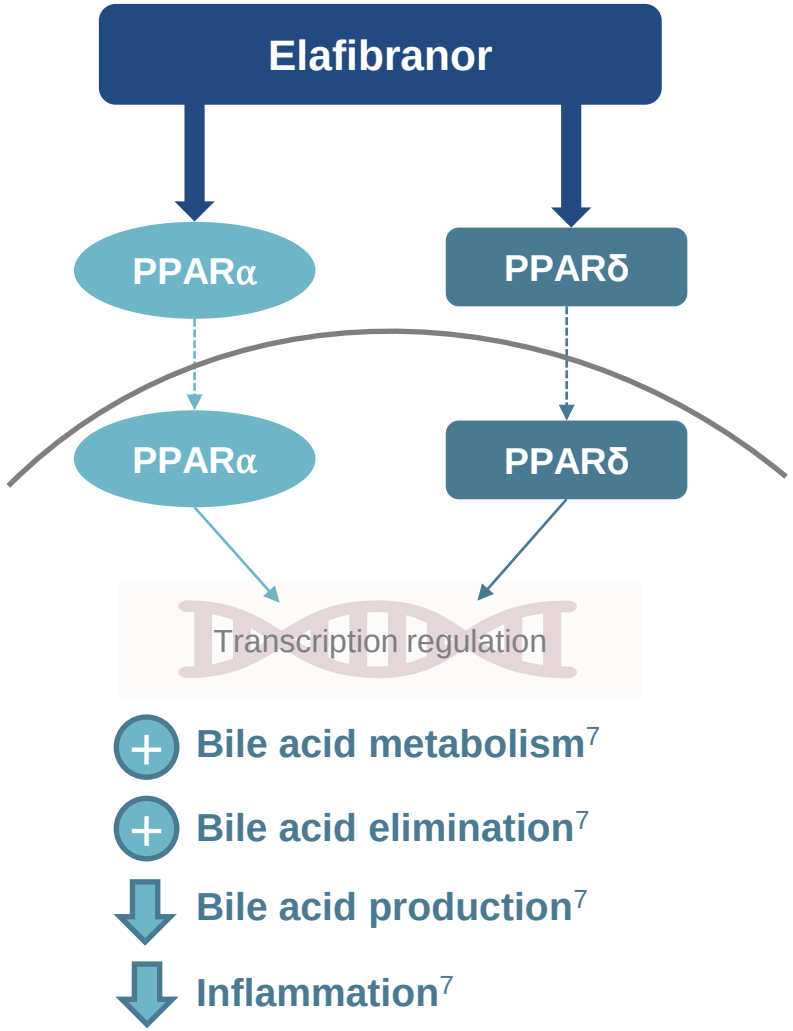
- **Ursodeoxycholic acid (UDCA)** and **obeticholic acid (OCA)** are the only currently licensed first-line and second-line treatments[2]

First-line: UDCA	Second-line: OCA
Up to **40%** of patients have an inadequate response[4]	Over **50%** of patients have an inadequate response[6]
3–5% are intolerant[5]	**Pruritus** may be exacerbated[6]

  - **Fibrates** (peroxisome proliferator-activated receptor [PPAR] agonists) are also used off-label as second-line treatment[2]

- **Elafibranor** is an investigational, oral, dual PPAR-α/δ agonist[7]

- In a **phase 2 trial** (NCT03124108), elafibranor significantly improved biochemical markers of cholestasis, improved symptoms of pruritus, and was well tolerated[7]



Adapted from Kytikova OY et al. 2020[8]

1. EASL. J Hepatol 2017;67:145–172; 2. Lindor KD. et al. Hepatology 2019;69:394–419; 3. Lv T. et al. J Gastroenterol Hepatol 2021;36:1423–1434; 4. Corpechot C. et al. Hepatology 2008;48:871–877; 5. Invernizzi P. et al. Dig Liver Dis 2017;49:841–846; 6. Nevens F. et al. N Engl J Med 2016;375:631–643; 7. Schattenberg JM. et al. J Hepatol 2021;74:1344–1354; 8. Kytikova OY et al. PPAR Research 2020;2020:8906968. OCA: obeticholic acid; PBC: primary biliary cholangitis; PPAR: peroxisome proliferator-activated receptor; UDCA: ursodeoxycholic acid.

Plain language slides:
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ELATIVE™ phase 3 trial objectives and design

ELATIVE™ | AASLD The Liver Meeting® Nov. 10-14, 2023
Presented by Dr Christopher L. Bowlus
#48490, AASLD 2023

ELATIVE™ aimed to evaluate the **efficacy and safety of elafibranor** in adult patients with PBC with an **inadequate response or intolerance to UDCA**

Screening and randomization

PBC and inadequate response or intolerance to UDCA (N=161)

- Alkaline phosphatase (ALP) ≥1.67x the upper limit of normal (ULN), and total bilirubin ≤2x ULN
- UDCA for ≥12 months (stable dose ≥3 months), or UDCA intolerant
- Randomization stratified by:
  - ALP >3x ULN or total bilirubin >ULN
  - PBC Worst Itch Numeric Rating Scale (NRS) score ≥4

Randomized-controlled trial

Randomization 2:1

- **Oral elafibranor 80 mg QD (n=108)**
- **Placebo (n=53)**

Primary endpoint analysis

Weeks: 4 | 13 | 26 | 39 | 52

Safety phone calls and study visits alternate every 26 weeks

Up to 104

Biochemical response at Week 52

Open-label extension (OLE)

Oral elafibranor 80 mg QD

Ongoing OLE

Up to 5 years

ALP: alkaline phosphatase; NRS: numeric rating scale; OLE: open-label extension; PBC: primary biliary cholangitis; QD: daily; UDCA: ursodeoxycholic acid; ULN: upper limit of normal.

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Study endpoints and assessments

Presented by Dr Christopher L. Bowlus
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Primary endpoint

1. Proportion of patients with **biochemical response** at Week 52, defined as ALP <1.67x ULN, with a reduction of ≥15% from baseline, and total bilirubin levels at or below ULN

Rank-ordered secondary endpoints

1. Proportion of patients with **normalization of ALP** at Week 52
2. Change in pruritus based on **PBC Worst Itch NRS** scores in patients with moderate- to-severe pruritus (baseline PBC Worst Itch NRS score ≥4) from baseline through **Week 52**
3. Change in pruritus based on **PBC Worst Itch NRS** scores in patients with moderate-to-severe pruritus from baseline through **Week 24**

Other secondary endpoints

1. Change in **ALP levels** from baseline to Week 52
2. Change in **PBC-40 Itch** and **5-D Itch** total scores in patients with moderate-to-severe pruritus from baseline to Week 52

- Safety and tolerability was assessed based on clinical assessments, laboratory evaluations, and reported adverse events

5-D: 5-Dimensional; ALP: alkaline phosphatase; NRS: numeric rating scale; PBC: primary biliary cholangitis; ULN: upper limit of normal.

Plain language slides:
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Baseline demographics and disease characteristics were well balanced between the groups

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Characteristic	Elafibranor (n=108)	Placebo (n=53)
Age at randomization, years, mean (SD)	57.5 (8.4)	56.4 (9.3)
Sex, female, n (%)	102 (94.4)	52 (98.1)
Race, White, n (%)	101 (93.5)	46 (86.8)
Time since diagnosis, years, mean (SD)	7.9 (5.9)	8.3 (6.8)
ALP, U/L, mean (SD)	**321.3 (121.9)**	**323.1 (198.6)**
>3x ULN,[a] n (%)	**43 (39.8)**	**20 (37.7)**
Total bilirubin, mg/dL, mean (SD)	0.57 (0.30)	0.55 (0.29)
>ULN,[b] n (%)	4 (3.7)	2 (3.8)
AST, U/L, mean (SD)	45.0 (24.2)	47.2 (32.8)
ALT, U/L, mean (SD)	49.3 (29.4)	50.3 (38.7)
GGT, U/L, mean (SD)	213.3 (186.1)	220.0 (220.3)
Concurrent UDCA treatment, n (%)	**102 (94.4)**	**51 (96.2)**
UDCA total daily dose, mg, mean (SD)	972.7 (239.9)[c]	1,027.0 (291.8)[d]
PBC Worst Itch NRS Score, mean (SD)	**3.3 (2.8)**	**3.2 (2.9)**
Moderate-to-severe pruritus (PBC Worst Itch NRS score ≥4), n (%)[e]	**44 (40.7)**	**22 (41.5)**
Liver stiffness, kPa, mean (SD)	9.9 (7.8)[f]	10.7 (8.9)[g]
>10.0 kPa and/or bridging fibrosis or cirrhosis on histology, n (%)	35 (33.7)[f]	19 (38.0)[g]
>16.9 kPa and/or cirrhosis on histology, n (%)	9 (8.7)[f]	7 (14.0)[g]

[a]ALP ULN values were 104 U/L in females and 129 U/L in males; [b]Total bilirubin ULN value was 20.5 µmol/L in females and males; [c]n=97; [d]n=50; [e]In patients with moderate-to-severe pruritus, mean PBC Worst Itch NRS score was 6.2 in the elafibranor group and 6.3 in the placebo group; [f]n=104; [g]n=50. ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; NRS: numeric rating scale; PBC: primary biliary cholangitis; SD: standard deviation; UDCA: ursodeoxycholic acid; ULN: upper limit of normal.

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Treatment with elafibranor led to a significant improvement in biochemical response at Week 52

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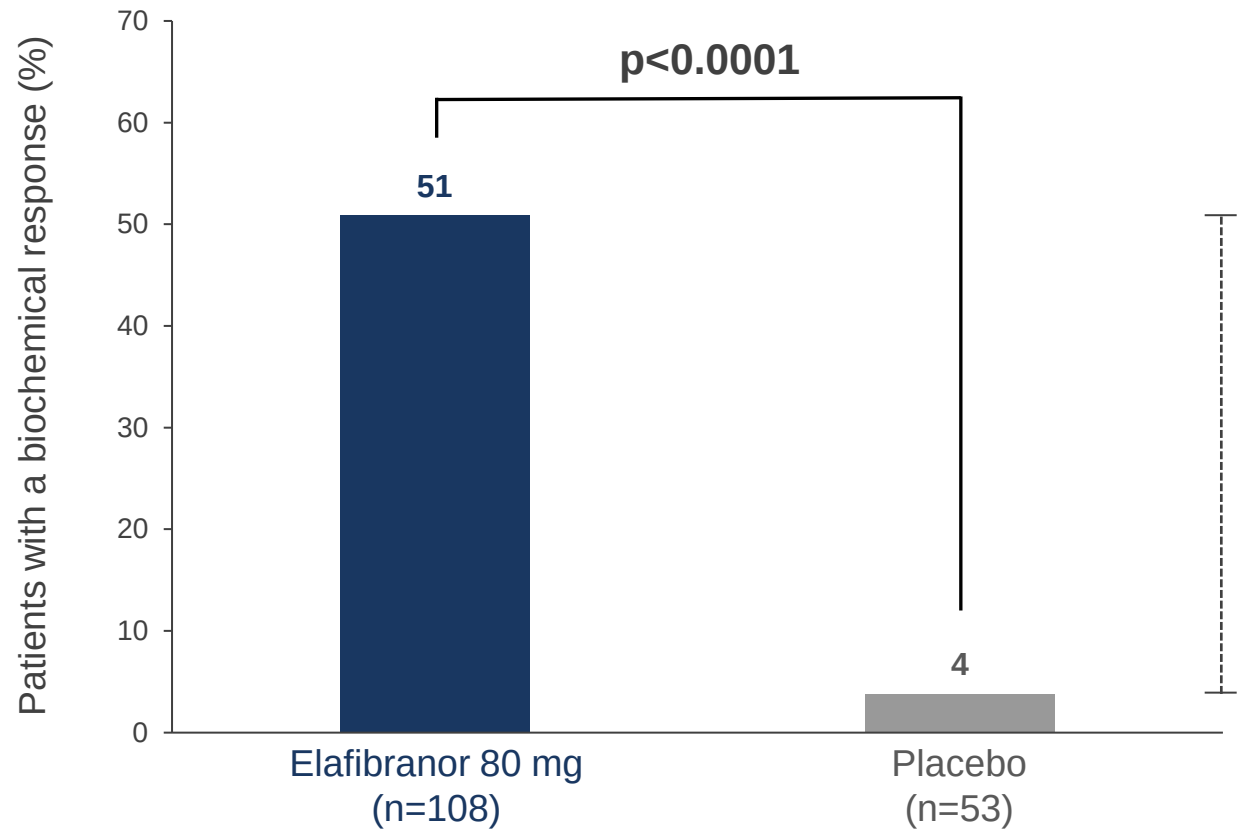

Treatment benefit: 47%

95% CI: 32% to 57%

Biochemical response was defined as a composite of ALP <1.67x ULN, with a reduction of ≥15% from baseline, and total bilirubin at or below the ULN

ITT population. P value was calculated using the Cochran-Mantel-Haenszel test stratified by the randomization factors. Non-response was imputed if patients discontinued treatment or used rescue therapy prior to Week 52, otherwise missing response was imputed using the closest non-missing assessment. ALP: alkaline phosphatase; CI: confidence interval; ITT: intent-to-treat; ULN: upper limit of normal.

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Only patients receiving elafibranor achieved normalization of ALP at Week 52

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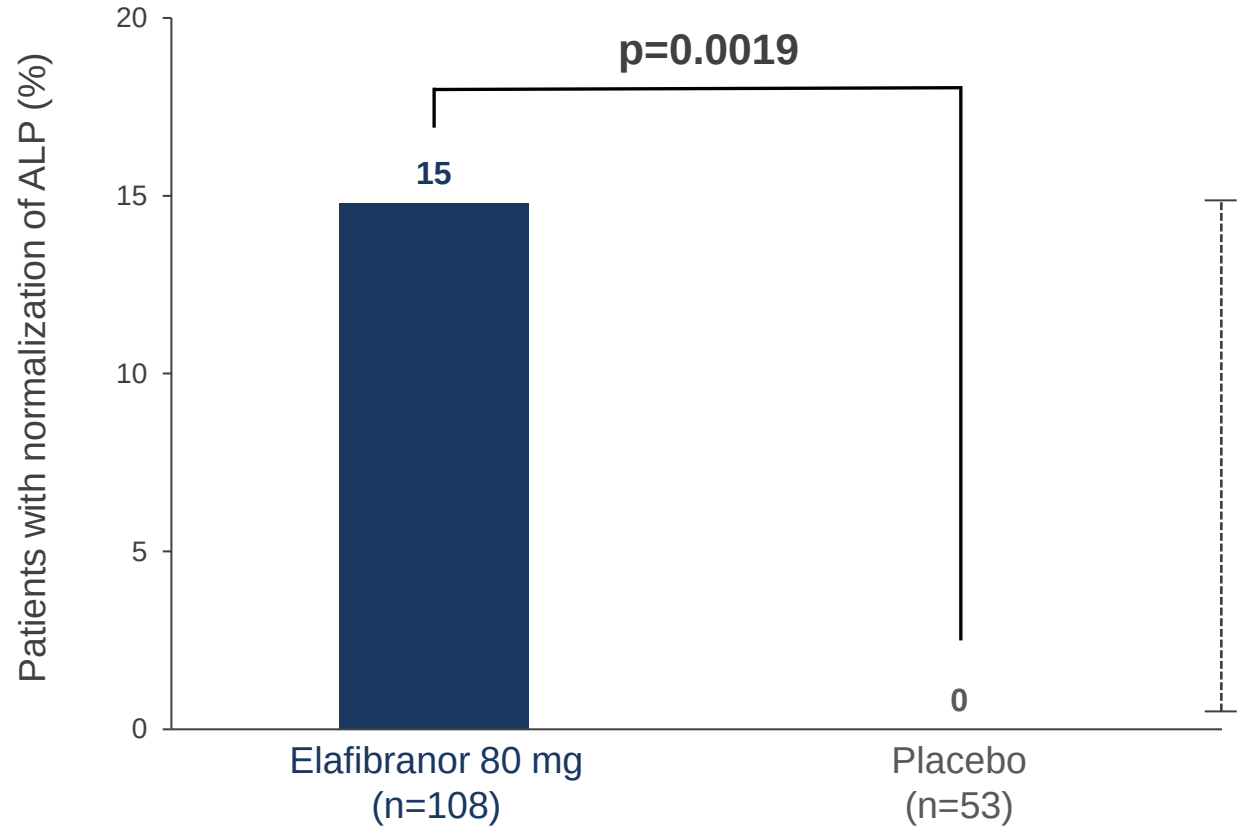

Treatment benefit: 15%

95% CI: 6% to 23%

ALP ULN: 104 U/L F, 129 U/L M

ITT population. P value was calculated using the Cochran-Mantel-Haenszel test stratified by the randomization factors. Non-response was imputed if patients discontinued treatment or used rescue therapy prior to Week 52, otherwise missing response was imputed using the closest non-missing assessment. ALP: alkaline phosphatase; CI: confidence interval; F: female; ITT: intent-to-treat; M: male; ULN: upper limit of normal. *Slides are the property of the presenting author and AASLD. Permission is required from both the presenting author and AASLD for reuse.*

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Reductions in ALP were observed as early as Week 4 and sustained through Week 52

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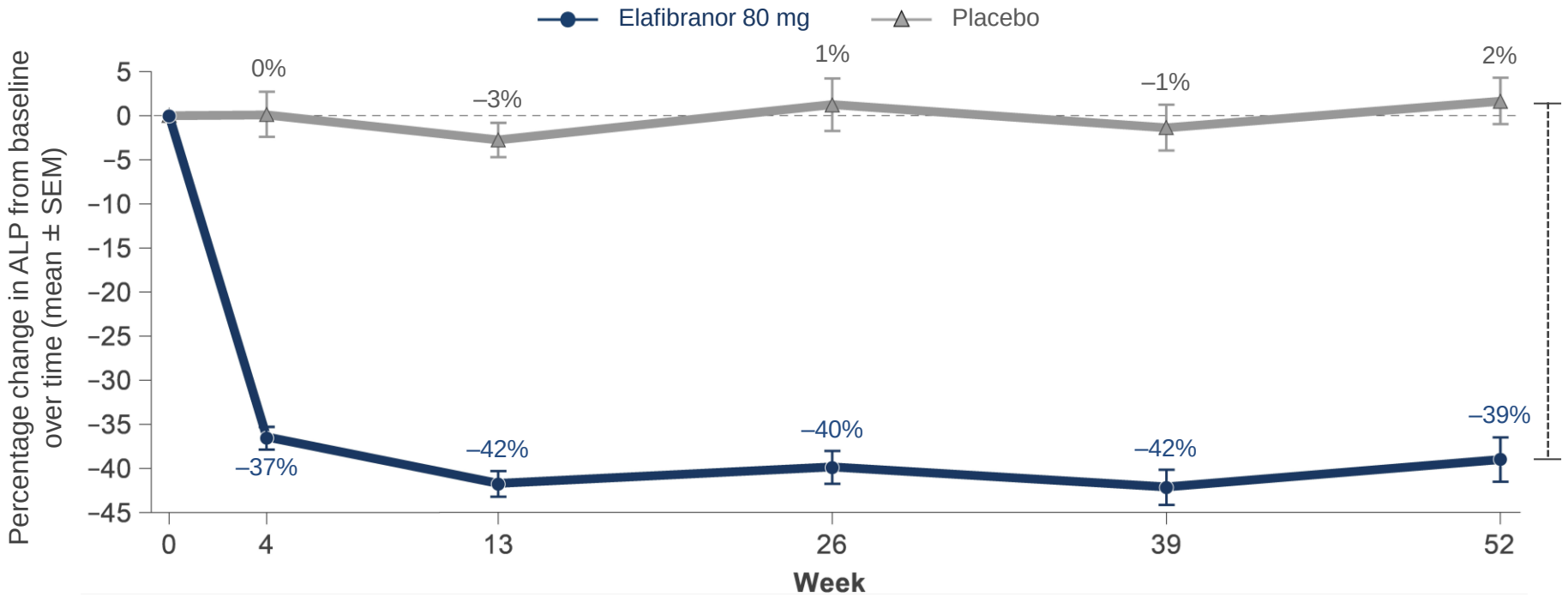

Treatment difference: –41%

95% CI: –48% to –33%

p<0.0001[a]

No. of Patients

Elafibranor	108	104	104	103	99	94
Placebo	53	48	48	47	47	47

ITT population. [a]P value is nominal. Data observed ≥1 day after patients discontinued treatment or used rescue therapy have been considered as missing data. The analysis of percentage change from baseline at Week 52 used a non-parametric randomization-based analysis of covariance method adjusting for baseline values. ALP: alkaline phosphatase; CI: confidence interval; ITT: intent-to-treat; SEM: standard error of the mean.

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Pruritus scales used in ELATIVE

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PBC Worst-Itch NRS[1]

Unidimensional scale that quantitatively measures the intensity of itch
- 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable)
- Assessed daily
- Recall period of 24 hours

PBC-40 Itch Domain[2]

Multidimensional tool specifically designed and validated for PBC
- Three-item questionnaire with each item scored from 1 to 5, higher scores indicating worse quality of life
- Assessed at each study visit
- Recall period of 4 weeks

5-D Itch[3]

Multidimensional tool assesses impact of itching on patients' lives
- Questionnaire consisting of 5 domains (duration, degree, direction, disability, distribution) for a total score ranging from 5 (no pruritus) to 25 (most severe pruritus)
- Assessed at each study visit
- Recall period of 2 weeks

5-D: 5-Dimensional; PBC: primary biliary cholangitis; WI-NRS; worst itch numerical rating score.

1. Vernon MK et al. J Patient Rep Outcomes 2021;5:134; **2.** Jacoby A et al. Gut 2005;54:1622–29; **3.** Elman S et al. Br J Dermatol 2010;162:587–93.

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A trend for improvement was observed in PBC Worst Itch NRS score, but did not reach statistical significance through Week 52

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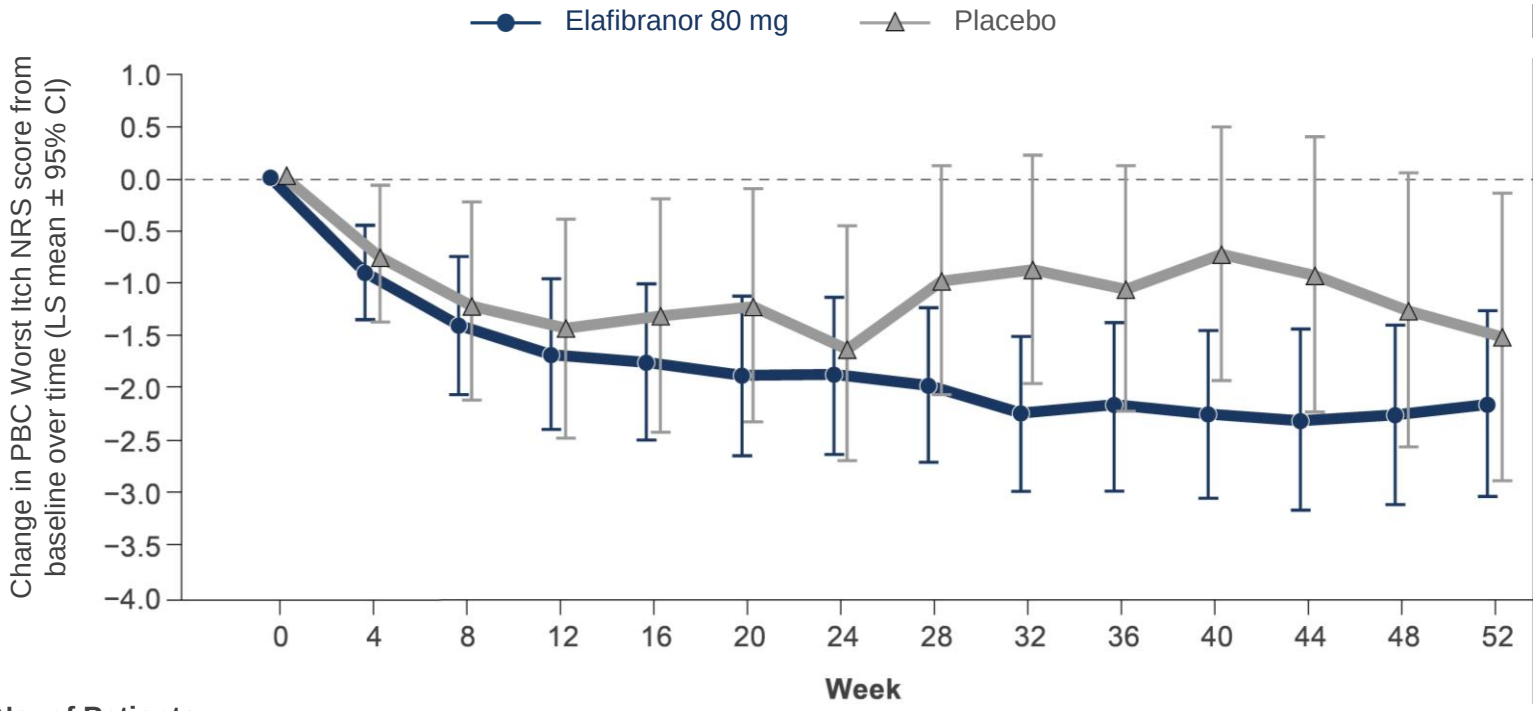
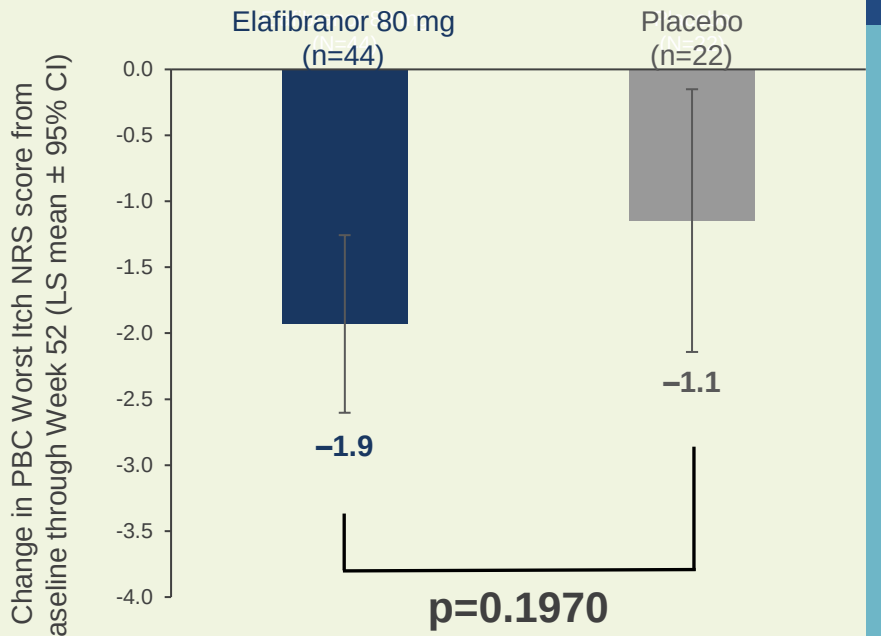
Change in PBC Worst Itch NRS by each 4-week period



No. of Patients

Elafibranor	44	41	40	39	40	38	37	34	35	34	32	34	35	32
Placebo	22	21	19	18	18	17	16	15	15	16	15	14	13	12

Change through Week 52



LS mean difference: –0.8

95% CI: –2.0 to 0.4

Data are shown for patients with moderate-to-severe pruritus (baseline PBC Worst Itch NRS score ≥4). Analyses used the mixed model for repeated measures with treatment, 4-week period and treatment by 4-week period interaction as fixed factors, and adjusted for baseline PBC Worst Itch NRS and the stratification factor of ALP >3x ULN or total bilirubin >ULN. ALP: alkaline phosphatase; CI: confidence interval; LS: least square; NRS: numeric rating scale; PBC: primary biliary cholangitis; ULN: upper limit of normal. *Slides are the property of the presenting author and AASLD. Permission is required from both the presenting author and AASLD for reuse.*

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Treatment with elafibranor improved pruritus based on the PBC-40 Itch score

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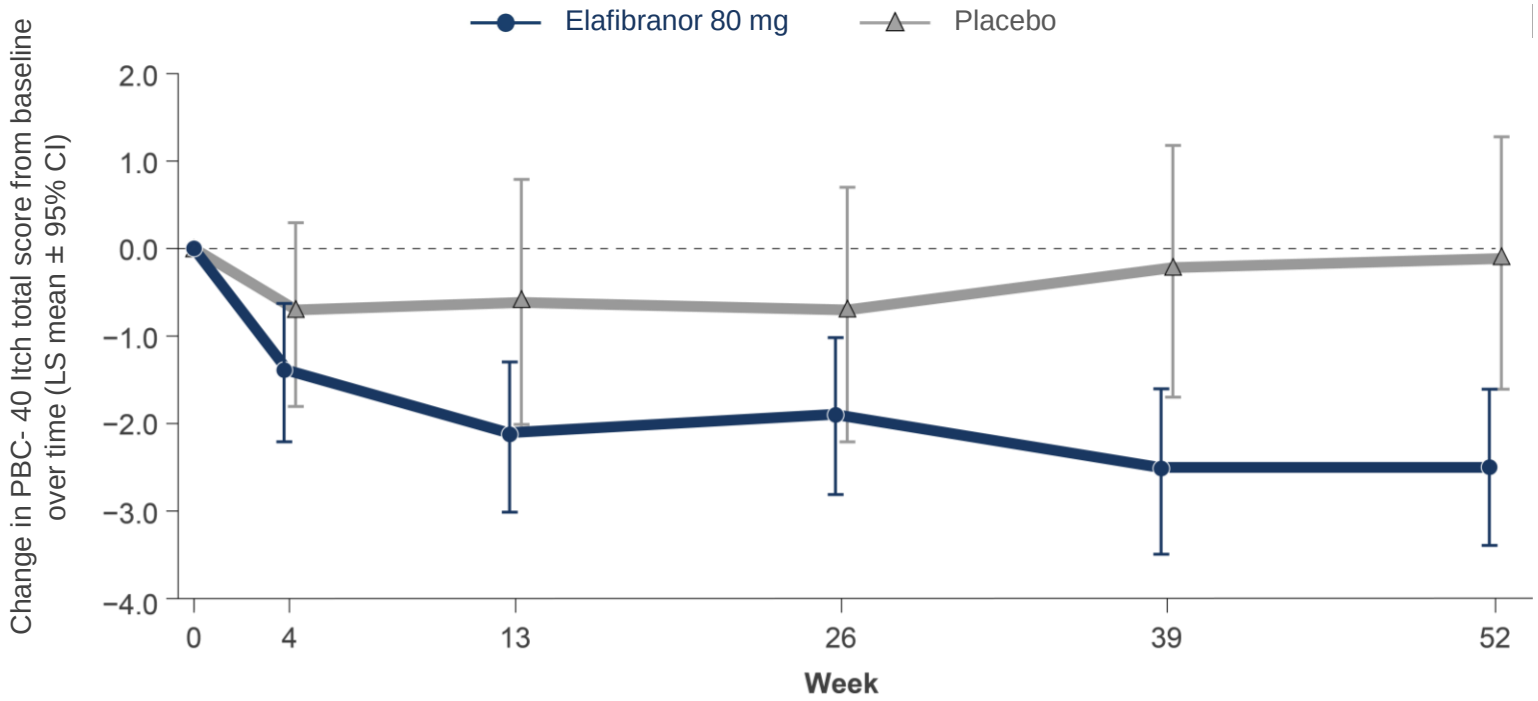
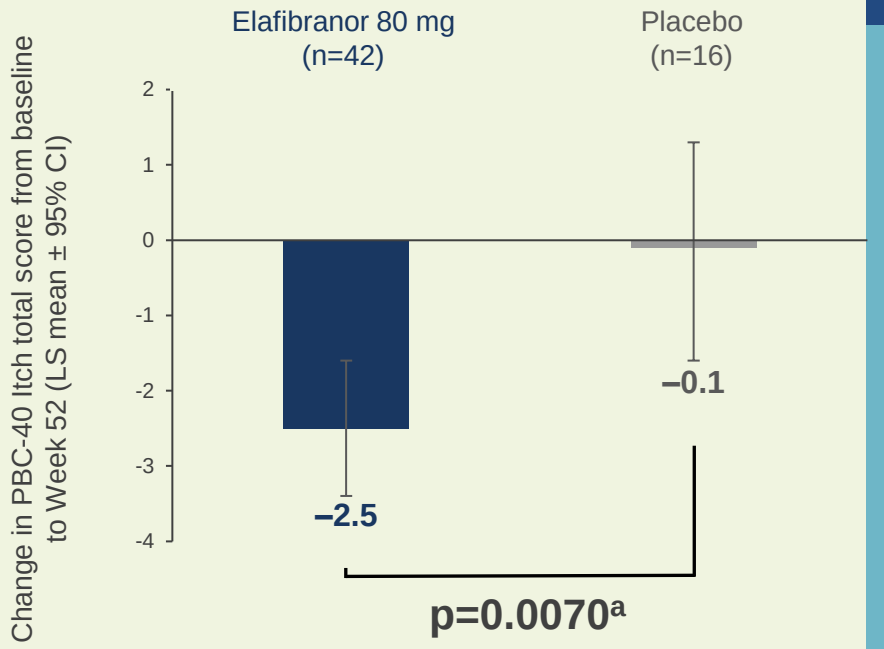
Change in PBC-40 Itch score from baseline



No. of Patients

Elafibranor	43	43	42	43	42	42
Placebo	21	20	17	15	16	16

Change at Week 52



LS mean difference: –2.3

95% CI: –4.0 to –0.7

Data are shown for patients with moderate-to-severe pruritus (baseline PBC Worst Itch NRS score ≥4). [a]P value is nominal. Analyses used the mixed model for repeated measures with treatment, visits (until Week 52) and treatment by visit interaction as fixed factors, and adjusted for baseline values and the stratification factor of ALP >3x ULN or total bilirubin >ULN. ALP: alkaline phosphatase; CI: confidence interval; LS: least square; NRS: numeric rating scale; PBC: primary biliary cholangitis; ULN: upper limit of normal. *Slides are the property of the presenting author and AASLD. Permission is required from both the presenting author and AASLD for reuse.*

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Greater reductions in 5-D Itch total score were also observed

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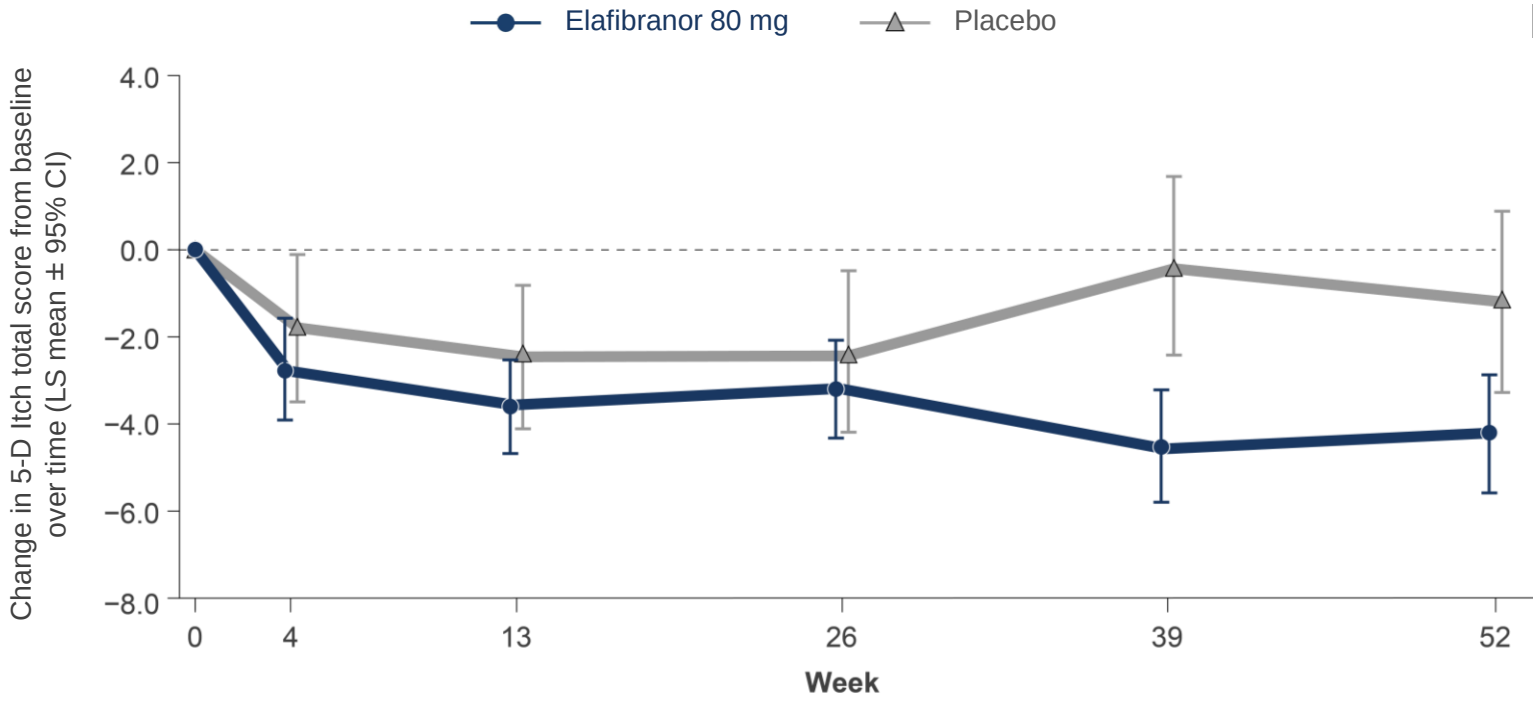
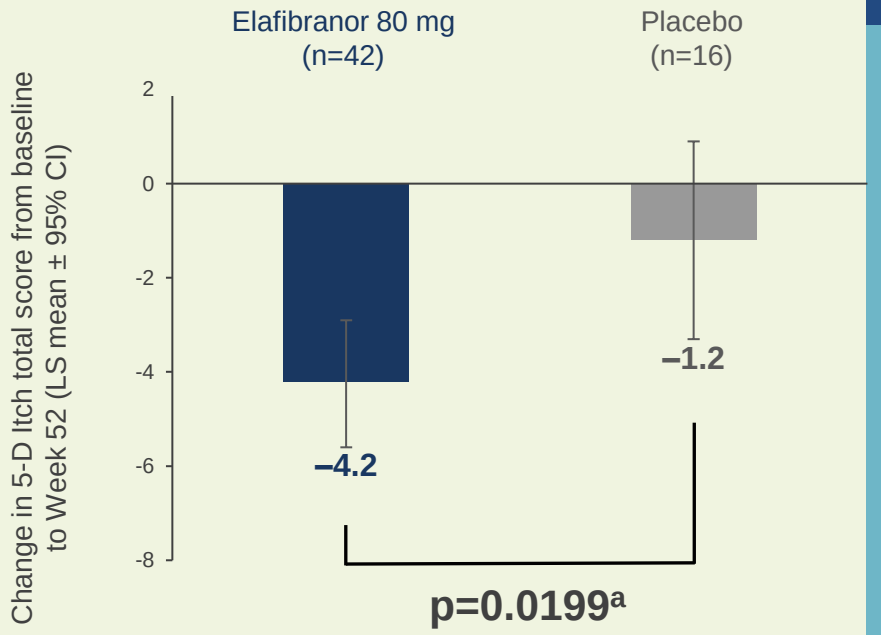
Change in 5-D Itch total score from baseline



No. of Patients						
Elafibranor	43	43	42	43	42	42
Placebo	21	20	17	15	16	16

Change at Week 52



LS mean difference: –3.0

95% CI: –5.5 to –0.5

Data are shown for patients with moderate-to-severe pruritus (baseline PBC Worst Itch NRS score ≥4). [a]P value is nominal. Analyses used the mixed model for repeated measures with treatment, visits (until Week 52) and treatment by visit interaction as fixed factors, and adjusted for baseline values and the stratification factor of ALP >3x ULN or total bilirubin >ULN. 5-D: 5-Dimensional; ALP: alkaline phosphatase; CI: confidence interval; LS: least square; NRS: numeric rating scale; PBC: primary biliary cholangitis; ULN: upper limit of normal. *Slides are the property of the presenting author and AASLD. Permission is required from both the presenting author and AASLD for reuse.*

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Elafibranor was generally well tolerated

Safety analyses were inclusive of all data up to Week 104

Event, n (%)	Elafibranor (n=108)	Placebo (n=53)
Any TEAE	**104 (96.3)**	**48 (90.6)**
Abdominal pain[a]	**12 (11.1)**	**3 (5.7)**
Diarrhea	**12 (11.1)**	**5 (9.4)**
Nausea	**12 (11.1)**	**3 (5.7)**
Vomiting	**12 (11.1)**	**1 (1.9)**
Any treatment-related TEAE	**42 (38.9)**	**21 (39.6)**
Any serious TEAE	**11 (10.2)**	**7 (13.2)**
Any severe TEAE	**11 (10.2)**	**6 (11.3)**
Acute kidney injury	**2 (1.9)**	**1 (1.9)**
Any TEAEs leading to treatment discontinuation	**11 (10.2)**	**5 (9.4)**
Blood creatine phosphokinase increase	**4 (3.7)**	**0**
Serious TEAEs leading to death	**2 (1.9)**	**0**
Treatment-related serious TEAEs leading to death	**0**	**0**

[a]Including upper and lower abdomen. Specific TEAEs displayed only are those occurring in >10% of patients treated with elafibranor with a >1% difference vs placebo. TEAE: treatment-emergent adverse event.

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Summary

Treatment with elafibranor led to a **significant improvement in biochemical response** compared with placebo at Week 52 (**51% vs 4%; treatment benefit 47%**)

- Reductions in ALP were **rapid and sustained** through Week 52
- Only patients treated with elafibranor achieved **ALP normalization**

Greater reductions in PBC-40 and 5-D Itch scores suggest that elafibranor may improve moderate-to-severe pruritus in patients with PBC

Elafibranor was generally **well tolerated** with an acceptable safety profile

Conclusions

Treatment with **elafibranor** led to significant improvement in **biochemical response**, along with **potential anti-pruritic benefits,** and was **generally well tolerated**

Elafibranor may provide an effective new **treatment for patients with PBC**

Biochemical response was defined as ALP levels of <1.67x ULN, with a reduction of ≥15% from baseline, and total bilirubin levels at or below the ULN. 5-D: 5-Dimensional; ALP: alkaline phosphatase; PBC: primary biliary cholangitis; ULN: upper limit of normal.

Plain language slides:
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David Loew

Chief Executive Officer

Elafibranor: central to expanding scope in Rare Disease

Rare cholestatic liver diseases

Bylvay® odevixibat

Launched in U.S.
PFIC + ALGS

Launched in E.U.
PFIC

BOLD Phase III trial in biliary atresia expected to read out in 2026

Elafibranor

Compelling data:
Phase III ELATIVE trial

U.S. & E.U.
regulatory submissions
anticipated this year

FOP

sohonos™ (palovarotene)

Regulatory approval
in U.S.

A breakthrough for
FOP community

First & only treatment
for patients with FOP

ALGS: Alagille syndrome; **PFIC**: progressive familial intrahepatic cholestasis;
PSC: primary sclerosing cholangitis; **FOP**: fibrodysplasia ossificans progressiva.

Conclusion

Elafibranor

Compelling Phase III results

A transformative potential treatment option for patients

Significant unmet medical need

Central to expanding Ipsen's scope in Rare Disease

IPSEN
Innovation for patient care

Focus. Together. For patients & society

QUESTIONS

THANK YOU

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